

Pleural tumors as sole primary manifestation of acute promyelocytic leukemia

A 66-year-old woman was admitted with progressive weakness, a weight loss of 22 pounds in the last 4 months, and diffuse thoracic pain. Laboratory analysis revealed anemia of 108 g/l, normal thrombocytes ($242 \times 10^9/l$) and normal leukocytes ($4.3 \times 10^9/l$). CT scan demonstrated four pleural tumors with up to 8 cm in diameter without evidence of disease elsewhere (Figure 1A, B). Bone scintigraphy indicated hot spots over the ribs on both sides. Biopsy of the pleural tumors showed cells staining positive for myeloperoxidase, CD34, CD43, CD45 and lysozyme, indicating myelogenous sarcoma (Figure 1C). Chromosomal translocations such as t(9;22) (BCR-ABL), t(8;21) (AML1-ETO), inv(16) (CBF β -MYH11), as well as mutations of the FLT3 gene were excluded by PCR in cells from the pleural tumors. Bone marrow biopsy was normal suggesting the diagnosis of an exclusively extramedullary manifestation of acute myeloid leukemia (AML) in the pleura. The patient was treated with two cycles of chemotherapy, including daunorubicin and cytarabine in the first cycle, and cytarabine alone in the second cycle. At the end of therapy, CT scan showed residual pleural tumors of up to 2 cm.

Five months later the patient reported costal pains again. CT scan demonstrated pleural tumors progressive in size and number. The patient was admitted because of nasal bleeding due to severe thrombocytopenia ($6 \times 10^9/l$). In addition, 64% of peripheral leukocytes ($8.2 \times 10^9/l$) were myeloid blasts. The bone marrow was highly infiltrated with myeloid blasts having an identical immunophenotype as the cells from the pleural tumors at diagnosis (Figure 1D, E). A relapse of AML was diagnosed and a therapy with hydroxyurea was initiated. The patient died 7 days later of pulmonary infection.

Surprisingly, the cytogenetic analysis at relapse (finished post mortem) indicated the presence of t(15;17) specific for the acute promyelocytic leukemia (APL) subtype of AML [1]. Retrospective analysis revealed that PML/RAR α transcripts were detectable in pleural tumors already at diagnosis (Figure 1F). However, bone marrow and peripheral blood at diagnosis were negative by PCR for PML/RAR α transcripts.

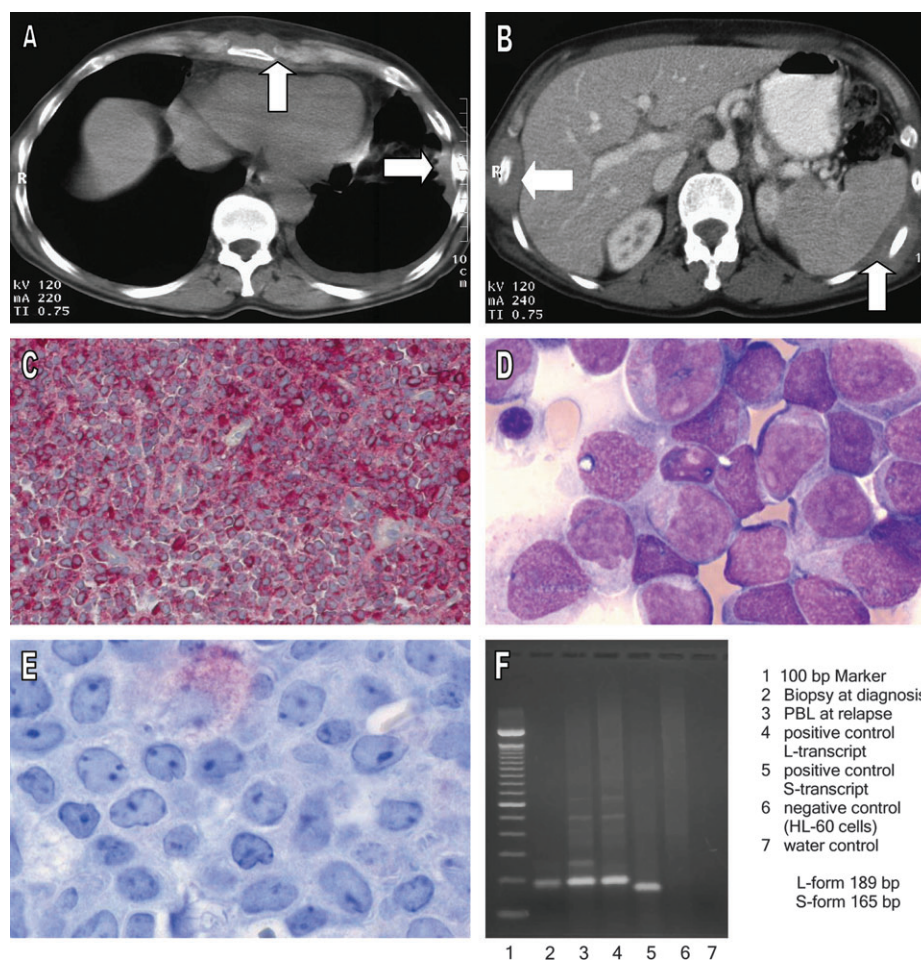


Figure 1. (A, B) CT scan at diagnosis showing large pleural tumors. (C) Pleural biopsy demonstrating blasts staining positive for myeloperoxidase, indicating granulocytic sarcoma. (D) Bone marrow aspirate and (E) bone marrow biopsy at relapse, indicating diffuse infiltration with myeloid blasts. (F) RT-PCR analysis detecting PML-RAR α transcripts in the pleural tumors at diagnosis (lane 2) as well as in leukemic blasts at relapse (lane 3).

Almost all cases of APL are defined at the molecular level by the presence of a balanced reciprocal translocation t(15;17) resulting in the PML-RAR α fusion gene [1]. APL is the most curable subtype of AML [2, 3]. With current therapy, including all trans retinoic acid (ATRA) and anthracycline-based chemotherapy, 70%–80% of patients are free of disease at 5 years [2, 3].

Extramedullary disease in APL may occur at relapse, but it is a very rare clinical event at diagnosis, with half of the reported cases involving the skin [4, 5]. Other sites involve the central nervous system, gingival, lymph nodes and spleen. To our knowledge this is the first report of pleural tumors as sole extramedullary manifestation of APL at diagnosis. Our case indicates that determination of t(15;17) should be included in the panel of markers assessed at diagnosis of all AML patients, including patients with exclusively extramedullary AML. This also allows timely diagnosis of APL at unusual clinical presentation and thus possibly life-saving therapy with ATRA.

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